Evaluation of Cardiovascular Outcomes among U.S. Workers Exposed to 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin

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Some animal studies and some human studies suggest that exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) may be associated with adverse effects on the cardiovascular system. As part of a cross-sectional medical study comparing workers employed 15 years earlier in the manufacture of 2,4,5-trichlorophenol or one of its derivatives at two U.S. chemical plants with an unexposed comparison group, we examined the association between TCDD exposure and various cardiovascular outcomes. A total of 281 workers and 260 unexposed referents participated. The workers had substantial exposure to TCDD, as demonstrated by significantly elevated mean serum TCDD concentration of 220 pg/g of lipid, compared with 7 pg/g of lipid among the referents. No significant association was found between TCDD exposure and any of the cardiovascular outcomes including myocardial infarction, angina, cardiac arrhythmias, hypertension, and abnormal peripheral arterial flow. Although our study had sufficient statistical power to detect an elevated risk for cardiac arrhythmias, hypertension, and abnormal peripheral arterial flow, it had low power (approximately 50%) to detect an elevated risk for myocardial infarction and angina. Our review of the literature suggests that our negative findings are consistent with those from other cross-sectional medical studies. Although several mortality studies of TCDD-exposed cohorts found significantly increased risks for cardiovascular disease mortality, similar increased risks were not observed in other mortality studies. The data available do not provide definitive conclusions but indicate that further examination of the association between TCDD exposure and cardiovascular disease should be pursued. — *Environ Health Perspect* 106(Suppl 2):635–643 (1998). *http://ehpnet1.niehs.nih.gov/docs/1998/Suppl-2/635-643calvert/abstract.html*

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Introduction

Dioxins are produced as unwanted contaminants during the combustion or production of chlorinated compounds. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is considered the most toxic of the dioxin congeners. Concern about the toxicity of this and other dioxinlike congeners continues to be widespread. Among the health concerns is cardiovascular toxicity.

Animal studies indicate that exposure to high doses of TCDD can produce effects on the cardiovascular system. These effects include ventricular dilatation (*1*), cardiac edema (*1,2*), valvulitis (*2*), myocardial degeneration (*3*), preatherosclerotic lesions in the aorta (*4*), and altered cardiac contractility (*5–8*).

Evidence for TCDD effects on the cardiovascular system in humans is conflicting. Case reports of TCDD-exposed individuals have described myocarditis (*9*), myocardial infarctions (*10,11*), ectasia of the coronary arteries (*12*), and rapidly progressive atherosclerosis (*13,14*). Four mortality studies of TCDD-exposed cohorts reported significantly elevated risks for cardiovascular disease mortality (*15–18*), whereas several others have not observed such elevations (*19–22*). Although several cross-sectional medical studies have also examined the association between TCDD exposure and effects on the cardiovascular system (*23–27*), statistically significant associations were found only in the study of U.S. Air Force Ranch Hand personnel responsible for spraying TCDD-contaminated Agent Orange in Vietnam (*27*). The Ranch Hands Study found statistically significant associations between TCDD exposure and peripheral pulse abnormalities of several arteries, medical record-verified hypertension, and one type of electrocardiogram (ECG) abnormality. In addition, findings from cross-sectional medical studies suggest that TCDD exposure may be associated with several risk factors for cardiovascular disease, including disorders of lipid metabolism (*27–29*), and glucose intolerance (*30*).

In this paper we report the cardiovascular findings from the largest cross-sectional morbidity study of TCDD-exposed industrial workers. These workers formerly were involved in production of 2,4,5-trichlorophenol (TCP) or one of its derivatives. Data were collected and analyzed to determine if TCDD exposure is associated with an increased risk for myocardial infarction, angina, cardiac arrhythmia, hypertension, and abnormal peripheral arterial flow.

Materials and Methods

In 1987, a cross-sectional medical study was undertaken to examine the long-term health effects of occupational exposure to chemicals and materials contaminated with TCDD. Details of the study design have been previously described (*31*). In summary, this study compared living individuals (workers) employed more than 15 years earlier in the production of TCP or one of its derivatives, which were

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Abbreviations used: 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; APAF, abnormal peripheral arterial flow; BMI, body mass index; CI, confidence interval; ECG, electrocardiogram; HDL, high-density lipoprotein; *ICD-9, International Classification of Disease, 9th revision*; mm Hg, millimeters of mercury; OR, odds ratio; RR, risk ratio; SE, standard error; SMR, standardized mortality ratio; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin TCP, 2,4,5-trichlorophenol.

substances contaminated with TCDD, with an unexposed comparison group. The workers were employed in one of two plants in Newark, New Jersey, and Verona, Missouri. Four hundred ninety workers were employed at the New Jersey facility from 1951 through 1969 in the production of TCP or one of its derivatives. At the facility in Verona, Missouri, 96 individuals were involved in the production of TCP or one of its derivatives. Production took place for approximately 4 months in 1968 and from April 1970 to January 1972. Both plants produced a variety of other chemicals, none of which are known or suspected cardiotoxins. To constitute the referent (comparison) group, one individual with no self-reported occupational exposure to TCDD-contaminated substances was sought from within the residential neighborhood of each worker; this individual matched the worker in age (within 5 years), race, and gender. The study protocol was approved by the National Institute for Occupational Safety and Health Human Subjects Review Board and informed consent was obtained from each of the participants.

Information on worker and referent health status was collected through a comprehensive set of standardized interviews and medical examinations. A lifetime medical history was elicited from each participant using interviewer-administered questionnaires. To reduce observer bias, all individuals conducting the medical histories, examinations, and tests were blind to the exposure status (worker or referent) of the participant. An interviewer-administered lifetime occupational history was elicited from each participant separate from the medical history. Duration of each job and length of occupational exposure to specific substances were recorded beginning with the participant's 16th birthday.

Blood was obtained from the participants after fasting and analyzed for TCDD (*32*), total cholesterol, triglyceride, high-density lipoprotein (HDL) cholesterol, and glucose. Two participants (one worker and one referent) did not have their blood drawn.

The medical examination consisted of a general physical examination (including blood pressure measurement in each arm while the participant was seated), Doppler examination of the peripheral pulses, chest X-ray, and ECG (Marquette Microcomputer Augmented Cardiograph II (Marquette Electronics, Milwaukee, WI). The computer interpretations of the ECG were reviewed blindly by board-certified cardiologists, who made corrections where appropriate.

The Doppler examination of the peripheral pulses involved measuring of ankle and arm pressures using a standard Baumonometer blood pressure bag and cuff and a Doppler ultrasonic instrument (Model 1010-LA, Parks Medical Electronics, Aloha, OR) while the participant was supine. The examination was divided into two parts: resting examination and postocclusion examination.

The resting examination involved bilateral blood pressure measurement at the brachial artery (arm blood pressure) and at the ankle (either the posterior tibial artery or the dorsalis pedis artery). The postocclusion examination involved inflating blood pressure cuffs that were placed around the participant's calves bilaterally to a pressure approximately 50 mm Hg higher than the maximal brachial pressure. After 5 min, both cuffs were deflated simultaneously and ankle blood pressures were measured bilaterally at both 1 and 2 min postocclusion. Generally, the dorsalis pedis artery blood pressure was measured at resting and postocclusion rather than the posterior tibial because of the dorsalis pedis ease of measurement. Measurement of the brachial blood pressure was repeated 3 min postocclusion.

Normally, ankle blood pressure should equal or slightly exceed arm blood pressure (*33*). The resting index has been derived to represent this relationship and was calculated by dividing the resting ankle pressure by the maximal resting brachial pressure. A resting index value of 0.97 or greater is considered normal. A value less than 0.97 is consistent with abnormal peripheral arterial flow (APAF) (*33*).

Because the resting index may not detect all cases of APAF, the postocclusion exam was included in our study. Including the postocclusion exam increases the sensitivity of detecting APAF (*33*). Normally, the ankle blood pressure at 1 min postocclusion should equal or slightly exceed the arm blood pressure. The recovery indices have been derived to represent this relationship. The recovery index 1 min postocclusion was calculated by dividing the ankle pressure at 1 min postocclusion by the maximal resting brachial pressure. The recovery index 2 min postocclusion was calculated similarly using the ankle pressure at 2 min postocclusion. A recovery index value of 0.97 or greater is considered normal. A value less than 0.97 is consistent with APAF (*34*).

Case Definitions

A participant was defined as having a history of myocardial infarction if the individual met one of two criteria. The participant either had to have reported that a physician had diagnosed this condition or had to have ECG evidence for a previous myocardial infarction. Similarly, a participant was defined as having a history of cardiac arrhythmia if the participant reported that a physician had ever diagnosed this condition, or if the participant had ECG evidence for an arrhythmia (an irregularity of heart rhythm including premature ventricular contractions, premature supraventricular contractions, ectopic beats, presence of a pacemaker, atrial fibrillation, atrial flutter, bradycardia [under 50/min], tachycardia [over 100/min] but excluding normal sinus rhythm). A participant was defined as having hypertension if one of the following three criteria was satisified: *a*) a self-reported history of physician-diagnosed hypertension; *b*) the lowest of two brachial artery systolic pressure readings taken while the participant was in sitting position exceeded 140 mm Hg (this is also the case definition for current systolic hypertension); or *c*) the lowest of two brachial artery diastolic pressure readings taken while the participant was in sitting position exceeded 90 mm Hg (this is also the case definition for current diastolic hypertension). A participant was defined as having APAF if either the resting index, the recovery index 1 min postocclusion, or the recovery index 2 min postocclusion was less than 0.97 in either leg. Finally, angina was defined as a self-reported history of physician-diagnosed angina. Participants were excluded from an analysis if they could not recall whether they had the disease of interest, if the self-reported onset of the disease of interest preceded the date of first exposure to substances contaminated with TCDD, or if the examination or test was not performed on the participant.

Analysis of Data

To evaluate the association between TCDD exposure and each of the cardiovascular outcomes and to evaluate for the presence of participation bias, unadjusted odds ratios (OR) were calculated and tested for significance using a chi-square test for association.

To evaluate the association between TCDD exposure and each of the cardiovascular outcomes of a priori interest

(myocardial infarction, angina, arrhythmia, hypertension, current systolic hypertension, current diastolic hypertension, APAF), logistic regression analyses were performed. The confounders that were examined in the regression analyses are described in detail elsewhere (*29*) and included years since last occupational TCDD exposure, age, race, gender, alcohol consumption history, employment at the New Jersey versus Missouri plant, body mass index (weight in kilograms divided by height squared in meters [BMI]), use of antihypertensive medications during the 2 weeks preceding the physical exam, cigarette consumption history, current diabeties, serum triglyceride concentration, serum total cholesterol concentration, serum HDL cholesterol concentration, family history of heart disease, occupational exposure to agents associated with cardiovascular effects (carbon monoxide, methylene chloride, lead, and carbon disulfide), and presence of pedal edema on physical exam.

In each model, the linearity assumption was checked for all continuous variables. Variables found to be nonlinear were stratified based on a priori cutpoints. Variables determined to be nonlinear in one or more models included BMI, triglyceride, HDL cholesterol, lipid-adjusted TCDD, half-life-extrapolated lipid-adjusted TCDD, and unadjusted TCDD.

Separate regression analyses were conducted using lipid-adjusted serum TCDD concentrations, half-life-extrapolated lipid-adjusted serum TCDD concentrations, or unadjusted serum TCDD concentrations. The half-life-extrapolated lipid-adjusted TCDD concentration is the estimated TCDD concentration when occupational TCDD exposure ceased and was calculated as described previously (*35*) to reflect the 7-year estimated half-life of the serum TCDD concentration (*36*). Because findings were similar for the analyses using the three different TCDD measurements, we report only the models using the lipid-adjusted TCDD concentrations. The workers were stratified into two groups based on lipid-adjusted serum TCDD concentrations: the quartile with the workers having the highest TCDD concentrations (238–3400 pg/g of lipid), and the three quartiles of workers with lower serum TCDD concentrations (< 138 pg/g lipid). Eight workers were excluded from these analyses because serum TCDD concentrations were not obtained. OR are provided, indicating the risk for the outcome of interest among each group of exposed workers compared to that for the unexposed referent group.

Potential confounders were retained in the final model if they created a meaningful difference in the coefficient of the exposure variable (more than a 15% difference) or if they were statistically significant for the outcome ($p < 0.05$). No significant interactions with TCDD exposure were observed. All models appeared to have adequate fit (*37*). All analyses were carried out using SAS procedures (SAS Institute, Cary, NC).

Results

Of the 586 workers at the two plants who were eligible for the study, 400 (68.3%) were living and could be located. A total of 142 (24.2%) workers were deceased and 44 (7.5%) could not be located. All 400 workers from the two plants who were living and could be located were invited to participate in the study; 281 (70%) were examined. A total of 938 referents were invited to participate in the study, of whom 260 (28%) were examined.

Descriptive information on the study cohort is provided in Table 1. Workers were found to have a statistically significantly elevated mean serum lipid-adjusted TCDD concentration (worker, 220 pg/g lipid [range, not detected, 3400 pg/g lipid; median, 68 pg/g lipid]; referents, 7 pg/g lipid [range, not detected, 20 pg/g lipid]; $p < 0.001$). Half-life-extrapolated lipid-adjusted serum TCDD concentrations were also elevated among workers (mean, 1900 pg/g lipid; median, 476 pg/g lipid). Overall, there were no statistically significant differences or a consistent pattern of differences between workers and referents for any demographic characteristics (age, race, gender, education, income) except for alcohol-years (alcohol-years are the average number of alcoholic drinks consumed per day multiplied by the number of years alcohol was consumed) . Referents were found to have a statistically significantly higher mean lifetime alcohol consumption (workers, 41.4 alcohol-years; referents,

Table 1. Characteristics of the study population by lipid-adjusted serum TCDD group.

	Referents (n=260)	Workers with lower serum TCDD[a] (n=208)	Workers with higher serum TCDD[b] (n=65)	All workers, (n=281)[c]
Mean age, years (SD)	56.0 (10.5)	53.2 (9.6)*	61.4 (10.0)*	55.4 (10.3)
White, %	88.9	88.0	92.3	88.9
Male, %	93.5	93.3	100*	95.0
Current drinker, %	63.1	64.4	63.1	64.4
Former drinker, %	23.9	27.9	26.2	27.1
Mean alcohol-years (SD)	62.1 (115.1)	40.9 (64.3)*	41.4 (60.3)*	41.4 (63.4)*
Current smoker, %	32.3	37.5	23.1	33.8
Former smoker, %	46.5	41.4	55.4	44.5
Mean pack-years (SD)	29.0 (32.4)	26.4 (28.3)	24.5 (24.8)	25.8 (27.3)
Plant 1, %	0	76.9*	83.1*	79.0*
Body mass index > 29, %	28.9	28.4	30.8	29.2
Use of antihypertensive medication, %	21.9	19.2	20.0	20.6
Family history of heart disease, %	50.6	51.9	53.2	52.5
Family history of hypertension, %	47.1	48.5	36.9	45.8
Current diabetic, %	6.2	8.2	15.4*	9.6
Serum triglyceride ≥ 250 mg/dl, %	7.3	8.2	6.2	7.5
Serum HDL > 35 mg/dl, %	86.9	84.6	80.0	82.9
Serum total cholesterol ≥ 240 mg/dl, %	32.3	37.5	24.6	33.8
Mean serum lipid adjusted TCDD, pg/g lipid (SD)	7 (2)	59 (59)*	730 (675)*	220 (434)*

[a]Serum TCDD < 238 pg/g lipid. [b]Serum TCDD ≥ 238 pg/g lipid. [c]The number of all workers is greater than the sum of the two subsets of workers (workers with lower and higher serum TCDD concentrations) because the group of all workers includes the eight workers for whom serum TCDD was not measured. *$p < 0.05$ unexposed referent group versus the group of exposed workers.

62.1 alcohol-years), which was attributed to seven referents with extremely high alcohol-year values. This was not considered an important difference because alcohol-years was found not to be a confounder in any of the analyses. Finally, workers in the quartile with the highest serum TCDD concentrations were older and had a higher prevalence of diabetes mellitus compared to the referent group.

Table 2 provides the results of the unadjusted analyses of the cardiovascular outcomes among workers and referents. Workers were not found to have a significantly elevated risk for any of the cardiovascular outcomes. Findings were similar when workers, stratified by lipid-adjusted serum TCDD concentration, were compared with the referent group.

Table 3 provides the results of logistic regression analyses for each of the cardiovascular outcomes. These analyses revealed that even after controlling for important confounders, TCDD exposure was not associated with an increased risk for myocardial infarction, angina, arrhythmia, hypertension, current systolic hypertension, current diastolic hypertension, or APAF. Even when the models were separately fitted with various parametric relationships for the lipid-adjusted serum TCDD concentration (linear, quadratic, log-transformed), TCDD was not significantly associated with any of the outcomes of interest. Furthermore, the findings for angina, current diastolic hypertension, and APAF are similar even after eliminating those variables (diabetes, triglycerides, and HDL cholesterol) found by some investigators to be possibly affected by TCDD exposure (i.e., potential intermediate variables). We found that age, gender, BMI, cigarette smoking, current diabeties, and a family history of heart disease were significant risk factors for two or more of these outcomes of interest.

Discussion

Our data do not support an association between long-term, high-dose TCDD exposure and any of several adverse cardiovascular outcomes. Although our data are consistent with other cross-sectional medical studies and some mortality studies of TCDD-exposed populations, data from four mortality studies suggest that TCDD exposure may be associated with an increased risk for cardiovascular disease mortality (*15–18*).

Two mortality studies of workers employed at pesticide-producing chemical plants showed positive dose–response associations between TCDD exposure and cardiovascular disease mortality (*16,18*). Flesch-Janys et al. (*16*) found significant trends between TCDD exposure and both cardiovascular disease (codes 390–459 from the *International Classification of Disease, 9th revision* [*ICD-9*]) and ischemic heart disease mortality (*ICD-9* codes 410–414). Those with the highest predicted half-life-extrapolated serum TCDD concentrations (345–3890 pg/g lipid) had the highest risk ratio (RR) for cardiovascular disease (RR = 1.96; 95% confidence interval [CI] = 1.15, 3.34) and ischemic heart disease (RR = 2.48; 95% CI = 1.32, 4.66). Hooiveld et al. (*18*) also found that those with the highest predicted half-life-extrapolated serum TCDD concentrations (121.5 pg/g lipid or higher) had the highest risk for circulatory system disease mortality (RR = 2.44; 95% CI = 1.34, 4.46) and ischemic heart disease mortality (*ICD-9* codes not provided) (RR = 3.70; 95% CI = 1.75, 7.80).

A study of Air Force personnel (the Ranch Hands Study) responsible for spraying Agent Orange, a TCDD-contaminated herbicide mixture, in Vietnam from 1962 to 1971 found an elevated risk for circulatory system disease mortality among nonflying enlisted personnel (*ICD-9* codes not provided) (standardized mortality ratio [SMR] = 1.6; 95% CI = 1.05, 2.35) but not among the entire cohort in the Ranch Hands Study (SMR = 1.05; 95% CI = 0.76, 1.42) compared to a nonexposed comparison group of Air Force veterans (*17*). Among the personnel in the Ranch Hands Study, the nonflying enlisted personnel had the highest current serum dioxin concentrations (*27*).

Another mortality study of a TCDD-exposed cohort found an increased risk for cardiovascular disease (*15*). Bertazzi et al. (*15*) studied the mortality of citizens in the Seveso region of Italy exposed to TCDD after an explosion at a trichlorophenol plant. For this study the Seveso region was divided into three zones named zones A, B, and R. Zone A had the highest TCDD contamination, zone R the lowest. Zone A males and females had an increased risk of death from nonmalignant disease of the circulatory system (*ICD-9* codes 390–459) (males: SMR = 1.75, 95% CI = 1.0–3.2; females: SMR = 1.89, 95% CI = 0.8–4.2). Zone R females also had a slightly increased risk of death from nonmalignant disease of the circulatory system (SMR = 1.15; 95% CI = 1.0–1.3). In addition, Zone R males had a statistically significant increased risk for death from chronic ischemic heart disease (*ICD-9* codes 412, 414) (SMR = 1.61; 95% CI = 1.2–2.2) and Zone R females from hypertensive heart disease (*ICD-9* codes 401–405) (SMR = 1.62; 95% CI = 1.0–2.8). Zone B residents did not have an increased risk of death from any disease of the circulatory system. Because the increased risk for cardiovascular disease mortality was observed principally within the first 5 years after the explosion, Bertazzi et al. (*15*) emphasized the role of disaster-related stressors. However, in light of the findings of Flesch-Janys et al. (*16*) and the Ranch Hands Study (*17*), the suggestion that stress was responsible for the Seveso findings needs to be reconsidered.

Several mortality studies of TCDD-exposed occupational cohorts did not find a significantly elevated risk for cardiovascular disease (*19–22*). However, comparison of findings across studies is difficult because of lack of consistency in the types of cardiovascular diseases that were reported. Furthermore, some of these studies are limited by small sample size (*19,20*) and lack of detailed exposure-response analyses (*20,22*). On the other hand, it should be noted that the SMRs for cardiovascular disease approached or exceeded 1.00 in many of these studies (*19,21,22*), suggesting the absence of a healthy worker effect. Because employed workers are healthier than the general population, the SMR for cardiovascular disease in employed populations is generally lower than 1 (*38,39*), although this differential disappears with longer follow up (*39*). The absence of a healthy worker effect in these TCDD-exposed cohorts may suggest a possible association between TCDD exposure and cardiovascular disease.

Several cross-sectional medical studies have also examined the association between TCDD exposure and effects on the cardiovascular system (*23–27*). Statistically significant associations were found only in the U.S. Air Force Ranch Hands Study (*27*). Although the overall conclusion from the study was that there was no apparent association between cardiovascular disease and TCDD exposure, an elevated risk was observed for peripheral pulse abnormalities of four leg arteries, medical record-verified hypertension, and nonspecific ST- and T-wave changes on ECG. It should be noted that the personnel participating in the U.S. Air Force Ranch Hands Study had lower serum TCDD concentrations (median 12.5 pg/g lipid, range 0–618 pg/g lipid) (*27*) than the workers we studied. The

Table 2. Distribution of the cardiovascular outcomes among workers and referents.

Outcome	Referents (n=260)			Workers with lower serum TCDD[a] (n=208)			Workers with higher serum TCDD[b] (n=65)			All workers (n=281)[c]		
	No. with outcome (%)	No. excluded[d]	OR[e] (95% CI)	No. with outcome (%)	No. excluded[d]	OR[e] (95% CI)	No. with outcome (%)	No. excluded[d]	OR[e] (95% CI)	No. with outcome (%)	No. excluded[d]	OR[e] (95% CI)
Myocardial infarction (includes those with self-reported and/or ECG diagnosis)[f]	20 (8)	2	1.00	20 (10)	2	1.28 (0.67, 2.45)	9 (14)	0	1.91 (0.84, 4.38)	31 (11)	2	1.49 (0.83, 2.68)
Myocardial infarction (self-reported only)	14 (5)	2	1.00	17 (8)	2	1.57 (0.76, 3.25)	7 (11)	0	2.10 (0.83, 5.36)	25 (9)	2	1.72 (0.87, 3.36)
Myocardial infarction (ECG diagnosis only)	12 (5)	0	1.00	11 (5)	0	1.15 (0.50, 2.67)	5 (8)	0	1.72 (0.59, 5.03)	17 (6)	0	1.33 (0.62, 2.84)
Angina (self-reported)	22 (8)	1	1.00	15 (7)	1	0.84 (0.43, 1.67)	6 (9)	0	1.10 (0.43, 2.83)	24 (9)	1	1.01 (0.55, 1.85)
Arrhythmia (includes those with self-reported and/or ECG diagnosis)[f]	35 (13)	2	1.00	25 (12)	3	0.89 (0.51, 1.53)	8 (12)	1	0.91 (0.40, 2.07)	34 (12)	4	0.89 (0.54, 1.48)
Arrhythmia (self-reported only)	18 (7)	2	1.00	14 (7)	3	0.98 (0.47, 2.02)	3 (5)	1	0.66 (0.19, 2.28)	17 (6)	4	0.87 (0.44, 1.73)
Arrhythmia (ECG diagnosis only)	21 (8)	0	1.00	13 (6)	0	0.76 (0.37, 1.55)	5 (8)	1	0.96 (0.35, 2.67)	19 (7)	1	0.83 (0.44, 1.58)
Hypertension (includes those with self-reported, current systolic, and/or current diastolic hypertension)[g]	107 (41)	11	1.00	93 (45)	7	1.14 (0.79, 1.66)	34 (52)	0	1.46 (0.84, 2.52)	131 (47)	7	1.22 (0.86, 1.72)
Hypertension (self-reported only)	58 (22)	11	1.00	45 (22)	7	0.95 (0.61, 1.48)	20 (31)	0	1.46 (0.80, 2.67)	68 (24)	7	1.09 (0.73, 1.63)
Current systolic hypertension	56 (22)	11	1.00	40 (19)	7	0.86 (0.54, 1.35)	22 (34)	0	1.76 (0.98, 3.18)	64 (23)	7	1.05 (0.70, 1.58)
Current diastolic hypertension	60 (23)	11	1.00	60 (29)	7	1.34 (0.88, 2.04)	16 (25)	0	1.03 (0.55, 1.94)	77 (27)	7	1.23 (0.83, 1.82)
APAF	45 (17)	4	1.00	30 (14)	0	0.79 (0.48, 1.31)	13 (20)	1	1.20 (0.60, 2.38)	45 (16)	1	0.89 (0.57, 1.41)

[a]Serum TCDD < 238 pg/g lipid. [b]Serum TCDD ≥ 238 pg/g lipid. [c]The number of all workers is greater than the sum of the two subsets of workers (workers with lower and higher serum TCDD concentrations) because the group of all workers includes the eight workers for whom serum TCDD was not measured. [d]Participants were excluded from the analysis if they could not recall whether they had the disease of interest, if the onset of the disease of interest preceded the date of first exposure to substances contaminated with TCDD, or if the examination or test was not performed on the participant. [e]The OR provides the risk for the outcome of interest among the group of exposed workers compared to that for the unexposed referent group. [f]Some participants had both a self-report and an ECG diagnosis of the outcome. Therefore, the sum of those with the self-reported outcomes and outcomes diagnosed by ECG will be more than the total number with the outcome. [g]Some participants met the criteria for more than one category of hypertension. Therefore, the sum of those with self-reported hypertension, systolic hypertension, and diastolic hypertension will be more than the total with hypertension.

Table 3. Parameter estimates from adjusted logistic regression models for myocardial infarction, angina, arrythmia, hypertension, and APAF.

	Beta	SE	OR	95% CI
Myocardial infarction[a]				
Workers with serum TCDD < 238 pg/g lipid	0.13	0.70	1.14	0.29, 4.49
Workers with serum TCDD ≥ 238 pg/g lipid	0.08	0.79	1.09	0.23, 5.06
Age, per year	0.07	0.02	1.07	1.03, 1.11
Per pack-year	0.02	4.7×10^{-3}	1.02	1.01, 1.03
Current alcohol drinker	−0.91	0.57	0.40	0.13, 1.23
Former alcohol drinker	0.30	0.57	1.35	0.44, 4.15
Family history of heart disease	0.97	0.36	2.63	1.30, 5.33
Employed at New Jersey plant	0.48	0.68	1.61	0.43, 6.06
No. observations, 521				
Hosmer and Lemeshow Goodness-of-Fit Test	4.35 with 8 degrees of freedom (p=0.82)			
Angina				
Workers with serum TCDD <238 pg/g lipid	−0.06	0.38	0.95	0.45, 1.98
Workers with serum TCDD ≥238 pg/g lipid	−0.40	0.53	0.67	0.24, 1.89
Age (greater than 55 years)	1.56	0.44	4.76	2.00, 11.36
HDL cholesterol (greater than 35 mg/dl)	−0.71	0.44	0.49	0.21, 1.16
Current diabeties	1.54	0.43	4.64	1.99, 10.85
Family history of heart disease	1.29	0.40	3.58	1.67, 7.86
No. observations, 522				
Hosmer and Lemeshow Goodness-of-Fit Test	10.24 with 8 degrees of freedom (p=0.25)			
Arrhythmia[a]				
Workers with serum TCDD <238 pg/g lipid	−0.03	0.28	0.98	0.56, 1.70
Workers with serum TCDD ≥238 pg/g lipid	−0.26	0.42	0.77	0.34, 1.78
Age (greater than 55 years)	0.82	0.28	2.27	1.31, 3.93
No. observations, 527				
Hosmer and Lemeshow Goodness-of-Fit Test	0.66 with 4 degrees of freedom (p=0.96)			
Hypertension[b]				
Workers with serum TCDD <238 pg/g lipid	0.29	0.21	1.34	0.89, 2.02
Workers with serum TCDD ≥238 pg/g lipid	0.05	0.30	1.05	0.58, 1.89
Age, per year	0.06	0.01	1.06	1.04, 1.08
BMI (greater than 29)	1.03	0.21	2.81	1.85, 4.28
Male gender	1.16	0.46	3.20	1.29, 7.94
Family history of hypertension	0.47	0.20	1.59	1.08, 2.34
No. observations, 506				
Hosmer and Lemeshow Goodness-of-Fit Test	11.34 with 8 degrees of freedom (p=0.18)			
Current systolic hypertension				
Workers with serum TCDD < 238 pg/g lipid	0.09	0.26	1.09	0.65, 1.83
Workers with serum TCDD ≥ 238 pg/g lipid	0.18	0.34	1.20	0.61, 2.34
Age, per year	0.11	0.01	1.12	1.09, 1.15
BMI (greater than 29)	0.92	0.25	2.51	1.52, 4.13
Caucasian race	−1.54	0.38	0.22	0.10, 0.45
Family history of hypertension	0.69	0.24	2.00	1.24, 3.23
No. observations, 506				
Hosmer and Lemeshow Goodness-of-Fit Test	5.83 with 8 degrees of freedom (p=0.67)			
Current diastolic hypertension				
Workers with serum TCDD < 238 pg/g lipid	0.30	0.22	1.35	0.88, 2.09
Workers with serum TCDD ≥ 238 pg/g lipid	−0.03	0.33	0.97	0.51, 1.87
Triglyceride (>250 mg/dl)	0.78	0.36	2.19	1.09, 4.40
BMI (greater than 29)	0.77	0.22	2.16	1.40, 3.32
Current alcohol drinker	1.04	0.43	2.83	1.21, 6.62
Former alcohol drinker	0.60	0.47	1.82	0.73, 4.56
Male gender	1.68	0.74	5.35	1.23, 23.28
No. observations, 514				
Hosmer and Lemeshow Goodness-of-Fit Test	1.51 with 7 degrees of freedom (p=0.98)			
Abnormal peripheral arterial flow				
Workers with serum TCDD < 238 pg/g lipid	−0.15	0.28	0.86	0.50, 1.51
Workers with serum TCDD ≥ 238 pg/g lipid	0.17	0.39	1.19	0.55, 2.55
Age, per year	0.04	0.01	1.04	1.01, 1.07
Per pack-year (square root)	0.22	0.06	1.24	1.11, 1.39
Serum cholesterol (per mg/ml)	7.1×10^{-3}	3.0×10^{-3}	1.01	1.00, 1.01
Current cigarette smoker	0.80	0.69	2.23	0.58, 8.59
Former cigarette smoker	0.40	0.63	1.49	0.43, 5.15
Caucasian race	−1.00	0.41	0.37	0.17, 0.82
Current diabeties	0.93	0.39	2.55	1.19, 5.47
No. observations, 527				
Hosmer and Lemeshow Goodness-of-Fit Test	5.90 with 8 degrees of freedom (p=0.66)			

Beta, parameter estimate. SE, standard error; pack-year, smoking one pack of cigarettes daily for 1 year. [a]Includes those with self-reported and/or ECG diagnosis of the outcome. [b]Includes those meeting any of the three criteria: self-reported hypertension, current systolic hypertension, or current diastolic hypertension.

half-life-extrapolated serum TCDD concentrations were also lower (median among personnel in the Ranch Hands Study having dioxin concentrations above background—130 pg/g lipid; range not provided) (*40*).

The Ranch Hands Study found that among the participants with a normal pulse examination in 1985, those with a current serum lipid-adjusted TCDD concentration greater than 10 pg/g lipid in 1992 had increased risk for abnormalitiesof the femoral pulse (RR = 3.35; 95% CI = 0.95, 11.8), popliteal pulse (RR = 4.86; 95% CI = 1.80, 13.10), dorsalis pedis pulse (RR = 1.70; 95% CI = 0.96, 2.99), and posterior tibial pulse (RR = 2.80; 95% CI = 1.39, 5.65) (*27*). In contrast, our study of workers who had higher serum TCDD concentrations compared to the those in the Ranch Hands Study did not find evidence of peripheral arterial disease. One explanation for this difference in findings may involve the techniques used to examine the lower extremity arteries. Our study used pressure indices whereas the Ranch Hands Study used Doppler waveform morphology. Pressure indices are the preferred noninvasive test for assessing the presence of peripheral arterial disease (*41*). Although Doppler waveform morphology can be useful as a supplemental test, interpretation of the test can be difficult and is prone to error due to Doppler equipment problems, poor operator technique, and certain pathologic and physiologic conditions (*42*). In future studies, consideration should be given to including both techniques for assessing peripheral arterial disease.

In addition, the Ranch Hands Study found a significant association between current lipid-adjusted TCDD concentration and both medical record-verified hypertension (RR for a 2-fold increase in TCDD = 1.14; 95% CI = 1.02, 1.28) and presence of nonspecific ST- and T-wave changes on ECG (RR for a 2-fold increase in TCDD = 1.20; 95% CI = 1.03, 1.40) (*27*). Several other cardiovascular outcomes examined in the Ranch Hands Study were found not to be associated with serum lipid-adjusted TCDD concentration. These included hypertension detected on examination, medical record-verified myocardial infarction, medical record-verified heart disease (not further specified), and other types of ECG abnormalities (excluding nonspecific ST-and T-wave changes). The U.S. Air Force Ranch Hands Study, therefore, does not provide definitive conclusions

because of inconsistent findings for related outcomes.

No statistically significant associations were observed in any of the other cross-sectional medical studies that reported cardiovascular outcomes (*23–26*). It should be noted that these other studies may have been limited by small sample size, and except for the study by Zober et al. (*26*), lack of detailed exposure–response analyses. Among 204 male 2,4,5-trichlorophenoxyacetic acid (2,4,5,-T) production workers, Suskind and Hertzberg (*23*) found no increased risk for self-reported hypertension, self-reported coronary artery disease, ECG findings, or atherosclerotic changes (not specified) on chest X-ray. Similarly, when Moses et al. (*24*) examined 116 male 2,4,5-T production workers with chloracne and compared them with workers not affected by chloracne, she found no increased risk for self-reported angina or self-reported myocardial infarction and no difference in the physical examination of the cardiovascular system. Bond et al. (*25*) found no increased association with self-reported hypertension among 27 workers involved in the production of TCP or among 87 workers involved in 2,4,5-T production. Finally, Zober et al. (*26*) did not find increased morbidity due to ischemic heart disease or other disorders of the circulatory system among 158 men who were exposed to TCDD after an uncontrolled decomposition reaction involving a TCP unit.

Cross-sectional medical studies may be less suitable for investigating severe or fatal disease such as cardiovascular disease because affected individuals often are not capable of participating in this type of study (*43*). We considered this participation bias as a possible explanation for why our study and other cross-sectional medical studies did not find an association between TCDD exposure and cardiovascular disease morbidity. For this explanation to be true, one would expect to see elevated cardiovascular disease mortality among the cohorts studied. The plants studied by Suskind and Hertzberg (*23*), Moses et al. (*24*), Bond et al. (*25*), and the two plants described here were included in a large cohort mortality study of U.S. workers involved in the production of TCDD-contaminated substances (*21*). This study by Fingerhut et al. (*21*). did not find an elevated risk for heart disease mortality (*ICD-9* codes 390–398, 402–404, 410–414, 420–429) (SMR = 0.96, 95% CI = 0.87–1.06), even among those with the highest durations of exposure (SMR = 0.87 among those with 15 or more years of exposure) (*44*). Findings were similar for ischemic heart disease (*ICD-9* codes 410–414) (SMR = 103) (*44*). Among workers at the two plants we studied, the SMRs for heart disease and ischemic heart disease were 1.07 and 1.06, respectively (*44*). These results suggest that participation bias may not be responsible for the findings in our study or in several other cross-sectional studies.

Furthermore, to assess the potential magnitude of participation bias in our study, a telephone interview was attempted with all the workers who would not consent to an examination, a 10% random sample of the referents who refused all participation, and all of the referents who provided lifetime occupational histories but refused to be examined. Of the 115 nonconsenting workers (excluding 2 who resided outside the United States and 2 who died between the first and this subsequent vital status determination) and 129 nonconsenting referents, 68 (57%) and 100 (78%), respectively, agreed to be interviewed by telephone. These individuals were asked questions similar to those asked in our medical study. The proportions of examined and nonconsenting workers reporting histories of myocardial infarction or angina were not statistically significantly different (Table 4). Similar results were found for the referents (Table 5). These results further suggest that participation bias may not be responsible for our study findings. We were unable to compare hypertension or cardiac arrhythmia because the questions asked about these conditions in the medical study differed from those asked in the telephone interview.

A possible limitation in this study is the low statistical power for examining some of the outcomes of interest. Although our study had sufficient power (80% or more) to detect a 1.5-fold elevation in risk for cardiac arrhythmias, hypertension, and APAF, our study had low power (approximately 50%) for detecting a similar elevation in risk for myocardial infarction and angina.

Although cross-sectional medical studies provide little evidence to support an association between TCDD exposure and cardiovascular disease, these studies have found associations with several risk factors for cardiovascular disease. Among the risk factors found to be associated with TCDD exposure were decreased HDL cholesterol serum concentrations (*27,29*), increased serum triglyceride concentrations (*27–29*), and glucose intolerance (*30*). There is some animal evidence to suggest that a TCDD-induced metabolic imbalance can lead to some of these risk factors. Enan et al. (*45*) found that TCDD-exposed guinea pigs have reduced glucose-transporting activity in the plasma membranes of adipose tissue and pancreas. In adipose tissue, reduced transmembrane glucose transport leads to suppressed lipoprotein lipase activity, and in the pancreas, to suppressed insulin production and release. These effects can lead to hypertriglyceridemia (lipoprotein lipase is responsible for metabolizing triglycerides absorbed from the gut) and glucose intolerance (insulin is needed for the metabolism of glucose), respectively, both of which are risk factors for cardiovascular disease. In

Table 4. Comparison of self-reported history of physician-diagnosed myocardial infarction and angina between examined and nonconsenting workers.

	Number of examined workers			Number of nonconsenting workers			
Outcome	Yes	No	Excluded[a]	Yes	No	Excluded[a]	Unadjusted OR (95% CI)
Myocardial infarction, self-reported	25	254	3	7	61	0	0.86 (0.33, 2.29)
Angina, self-reported	24	256	1	2	66	0	3.09 (0.68, 12.54)

[a]Participants were excluded from the analysis if they could not recall whether they had the disease of interest.

Table 5. Comparison of self-reported history of physician-diagnosed myocardial infarction and angina between examined and nonconsenting referents.

	Number of examined referents			Number of nonconsenting referents			
Outcome	Yes	No	Excluded[a]	Yes	No	Excluded[a]	Unadjusted OR (95% CI)
Myocardial infarction, self-reported	14	254	2	9	91	0	0.58 (0.23, 1.51)
Angina, self-reported	22	237	1	6	94	0	1.45 (0.54, 4.15)

[a]Participants were excluded from the analysis if they could not recall whether they had the disease of interest.

support of this hypothesis, two animal studies have shown that TCDD causes suppressed lipoprotein lipase activity (*4,46*). Because the origin and metabolism of HDL is not as well understood compared with that of other lipoproteins, the mechanism by which TCDD affects HDL metabolism cannot be determined at this time.

In conclusion, our study found that workers with high occupational TCDD exposure at least 15 years earlier, many of whom continued to have persistently elevated TCDD body burdens, had no significantly increased risk for any of the cardiovascular outcomes we investigated. Our findings are consistent with those of other cross-sectional medical studies of TCDD-exposed individuals. Although several mortality studies of TCDD-exposed cohorts found an increased risk for cardiovascular disease mortality, other mortality studies did not have similar findings. The data available do not provide definitive conclusions but indicate that further examination of the association between TCDD exposure and cardiovascular disease should be pursued.

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